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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	41

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/913,918	Prokop
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 15, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *69-71, 77, 97-108, 112, and 113* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *69-71, 77, 97-108, 112, and 113* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 30
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 76, 78-96, 109-111 have been canceled, claim 113 has been added by the amendment filed November 13, 2002.

Claims 69-71, 77, 97-108, 112, 113 are pending.

The specification is objected because the first paragraph of the specification does not contain a cross-reference information with respect to the parent case 08/422,066 and its updated status, to which application this instant application claims priority under 35 USC 120.

Elected claims 69-71, 77, and 97-108, 112, 113 readable on the species of osteoporosis and obesity factor, to which following grounds of rejection are applicable, are pending for examination.

To the extent that claims 69 and 77 are readable on isolated genetically modified stromal cells expressing an obesity factor, wherein the only the intended use of the implantable cells is to control obesity in any mammal, the new ground of rejection under 35 USC 112, first paragraph is applicable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69 and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A container containing an isolated marrow stromal cell which comprises an expressible gene construct encoding the protein,

wherein the container physically isolates the stromal cell from immune cells of the animal, and

wherein the container has pores which permit diffusion of the protein between the interior and exterior of the container.

The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to use the invention to express any obesity factor in any animal in order to control obesity in the animal.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The application indicates that implantation of mesenchymal cells from normal mice into irradiated transgenic mice that expresses the mutated COL1 A1 gene led to production of progeny cells that express the normal proα(1) chains in the irradiated mice. The application further contemplates that long-term expression of any therapeutic protein encoded DNA including the obesity gene (Ob) can be achieved for therapeutic application of the gene in the treatments of obesity or decrease of appetite in any animal by using any autologous or non-autologous stromal cell (not necessarily limited to mesenchymal cells (MSC)) having any Ob expressing DNA vector incorporated therein.

While the application including the state of the prior art provides sufficient guidance and reasonable enablement for an improved methods of using claimed container to express a recombinant protein for non-therapeutic applications that are well known to a skilled artisan at the time the invention was made, the application on the basis of applicant's disclosure does not provide any reasonable enablement including sufficient guidance and/or factual evidence so as to reasonably extrapolate from a simple production of endogenous COL1 A1 proteins by allogeneic MSC in transgenic mice expressing the mutated COL1 A1 protein to any therapeutically relevant effect in any animal having a real-world medical disease associated with obesity, particularly given that *ex vivo* gene therapy of using bone marrow stromal, stromal stem cells or mesenchymal stem cells is an emerging technology that remains reasonably unpredictable at the time the invention was made (see Marshall (Science, Vol. 269, pp. 1050, 1995), Verma *et al.* (Nature, Vol. 389, pp. 239-242), Anderson (Nature, Vol. 292, 25-30, 1998), Moritz *et al.* (J. Clin. Invest. 1994, 93:1451-1457),

Riddell *et al.* (Nature Medicine, Vol. 2, 2:216-223, 1996), Onodera *et al.,* Acta Haematologica, 101, 2, pp. 89-96, 1999, Kohn , Current Opinion in Pedatrics, 7, 56-63, 1995).

The specification does not provide reasonable enablement for claims encompassing *ex vivo* gene therapy methods as claimed, wherein any administration route is employed, wherein any genetically modified stromal stem cell is employed, and wherein obesity as disclosed in the claims is contemplated.

More specifically as to the state of the art of *ex vivo* gene therapy of using bone marrow stromal cells including stromal stem cells, the state of the art exemplified by Marshall (Science, Vol. 269, pp. 1050, 1995) indicates that in 1995, "so far, there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" and that "while there are several reports of convincing gene transfer and expression, there is still little or no evidence of therapeutic benefit in patient or even in animal models" (page 1050). More specifically as the unpredictability of using retroviral vectors which has been preferably used in experimental protocols *in vitro* and/or *in vivo,* due to its ability to better express a recombinant protein in stem cells as compared to other viral or non-viral vectors, Verma *et al.* (Nature, Vol. 389, pp. 239-242) teach that "another formidable challenge to the *ex vivo* approach is the efficiency of transplantation of the infected cells" and that "successful animal models will prove inadequate when the same protocols are extended to humans" (page 240, column 3, last paragraph). The specification, for example, contemplates that by employing any retroviral trasnduced MSC as carrier of protein drugs in any *ex vivo* gene therapy method, the stem cells would function as a continuous supply of protein drugs to any target site *in vivo,* such that any disease or disorder can be treated therapeutically in any animal. A skilled artisan, attempting to make and use the claimed constructs, would first look to the specification for guidance as to which therapeutic protein drug encoded DNA to use in an *ex vivo* gene therapy wherein retroviral transduced bone marrow stromal or stromal stem cells are employed for treating a disorder. However, the state of the prior art of record indicates that there are many problems to be overcome before all vector systems including retroviral vectors effect a contribution to medicine. Next, the artisan would look to the specification for guidance as to which compositions among the disclosed compositions, *e.g.,* genetically modified cells expressing any protein, receptor, or enzyme for use in for the intended purpose of achieving a therapeutic

effect as the result of protein drug expression, the specification provides little guidance for one skilled in the art to determine, without undue experimentation, as to which of the genetically modified stromal stem cell exhibit the intended "protein drug" effect in any animal having a disease, disorder, or condition as contemplated by the as-field specification.

More specifically with respect to claims directed enzyme therapy in the context of *ex vivo* gene therapy, even after 10 years from the effective filing date, Anderson (Nature, Vol. 292, 25-30, 1998) with respect to an experiment study on human ADA patients wherein autologous T cells are employed as carriers of ADA transduced retroviral vectors states that "although both girls have gene-engineered T lymphocytes in their circulation after more than 7 years, no definitive conclusion after more than 7 years, no definitive conclusion can be drawn as to the relative roles of PEG-ADA and gene therapy in their excellent clinical course". The fact that no working examples have been shown by the as-filed specification to conclusively show a therapeutically relevant effect in an animal having a real world medical condition associated with a protein defect, coupled with the unpredictability of gene therapy as expressed by the art of record, does not provide sufficient evidence for a skilled artisan to reasonably extrapolate, without any undue experimentation, from the basis of applicant's disclosure to any therapeutically useful effect by using any protein encoded vector contained in any bone marrow stromal cell encapsulated by any container as contemplated by the claimed invention.

While the as-filed specification indicates that by using a container known in the prior art, *e.g.,* diffusion chambers, polymeric capsule, the genetically modified bone marrow stromal cells will be insulated or physically isolated from an immune response, thereby contemplating that a therapeutically relevant effect can be generated by the cells due to the protection of the administered stromal stem cells by any container from the immune response of the treated animal. However, in addition to *in vivo* transient gene expression by an expression vector and the destruction of the diffused stromal stem cells by the immune response before the cells produce a sufficient amount of protein at a desire target site to produce a therapeutically relevant effect, Riddell *et al.* (Nature Medicine, Vol. 2, 2:216-223, 1996) reaffirmed the unpredictability of *ex vivo* gene therapy methods wherein foreign cells and/or proteins are employed at the

time the invention was made by indicating that even with the use of autologous cells expressing a foreign protein, HIV-infected patients when grafted with autologous cytotoxic CD8+ T cells induce strong primary T-cell immune responses to foreign antigens expressed by transferred autologous cytotoxic CD8+ T cells (p. 221, column 1), and that the rejection of genetically modified cells and/or foreign proteins by even immunocompromised hosts suggests that *ex vivo* gene therapy by using foreign protein expressed transiently by even autologous cells is not routine or conventional in the prior art at the time the invention was made.

In addition, it is not clear how the systemic administration of genetically modified bone marrow cells which harbor a foreign receptor on the cell surface, for example, would not be destroyed by the immune response that is mounted against the foreign receptor expressed on the surface of the genetically modified cells after their diffusion from the container. Even if some of the genetically modified stromal stem cells and/or recombinant proteins escape from the immune response in a survived host after an administration or implantation, it is further not apparent how the genetically modified stromal stem cells traverse though barriers such as peripheral vein and endothelial wall to reach a disease site so as to generate a therapeutically relevant effect. Note also that Hoeben *et al.* (Human Gene Therapy, 4, 179-186, 1993) provides factual evidence showing that even if the genetically modified implanted fibroblast cells expressing a therapeutic protein, *e.g.,* factor VIII, survive the immune response of a recipient mouse which is immuno-deficient, there is no evidence of any recombinant Factor VIII in the plasma samples of recipient mice (abstract). The absence and/or *in vivo* transient expression of a recombinant protein in even a small animal such as immuno-deficient mice, and a rapid clearing of the introduced recombinant protein from mouse's serum as shown in the prior art of record, does not lend any credible evidence to support applicant's claim that any stromal stem cell when carrying a protein drug encoded vector can be employed as a stable bioreactor to provide a continuous supply of protein drugs in any animal having any disease or disorder, such that a therapeutically relevant effect can be generated. Thus, where *ex vivo* gene therapy using any coding sequence of any protein is not reasonably predictable in establishing a therapeutic outcome of gene therapy for all types diseases, the gene therapy methods referred to in the present claims are also not

predictable, nor is it apparent as to how a simple expression of endogenous protein from non-genetically modified MSC in transgenic mice as exemplified in the specification is reasonably correlated to a therapeutic effect in any animal having any disease as claimed.

Furthermore, the state of the art exemplified by Moritz *et al.* indicates that *ex vivo* gene therapy using genetically modified cell for engraftment into any an animals remain unpredictable. More specifically, the Moritz *et al.* reference (J. Clin. Invest. 1994, 93:1451-1457) indicating that "although gene transfer and long term gene expression in repopulating stem cells have been achieved in murine models by a number of investigators, *in vivo* experiments in larger animals such as dogs and primates have met with limited success, largely because of the low efficiency of infection of primitive hematopoietic stem cells"

The art of record clearly indicates that the efficiency of gene transfer into stem cells was much lower when similar protocols were assessed in large mammals and in human gene therapy trials, suggesting that there are species-specific differences in the susceptibility of stem cells to retrovirus infection. There are no working examples in the specification, which indicates the efficiency of vector transduction in any stromal stem cell of any mammal including humans wherein a therapeutic effect is generated. Thus, in absence of any *in vivo* data regarding the grafting methods in any and/or all animals other than a murine model, it is not apparent how one skilled in the art determines the appropriate combination of transfection method, level of expression, cell numbers and method of administration for each possible gene, so as to have a therapeutic effect in any and/or all animals, without undue experimentation.

More specifically as to the state of the art of *ex vivo* gene therapy of employing any genetically modified hematopoietic cell expressing a transgene coding for an Ob protein, Onodera *et al.,* Acta Haematologica, 101, 2, pp. 89-96, 1999, indicates that even in 1999, the retroviral-mediated gene transfer to hematopoietic stems was insufficient for achievement of any therapeutically relevant effect (abstract). To further complicate the subject matter in the treating obesity by using an Obese factor, Considine, J. Clin. Invest. Vol. 95, pp. 2986-2988, 1995 provides evidence that the mutations present in the mouse *ob* gene are not present in obese humans (p. 2986). More specifically, Considine states:

> In summary, *ob* gene expression in humans, as in mice, appears to be limited to the adipoctye. However, unlike the mouse model, no lack of message or flawed message was detected in the human subjects. Additionally, *ob* gene expression was highly correlated with BMI [body mass index]. Further work is necessary to elucidate the exact role of the *ob* gene in human obesity.

Thus and insofar as the claimed carrier expressing an obesity factor to treat obese human patients, which appears to be the only real-world use of the claimed product, particularly on the basis of the as-filed specification and the totality of the prior art, it is not apparent how a skilled artisan could reasonably extrapolate a simple expression of any obese factor to a therapeutically relevant effect in the treatment of obesity in obese patients, let alone all of other problems of *ex vivo* gene therapy as set forth above by other art of record.

Moreover, Kohn , Current Opinion in Pedatrics, 7, 56-63, 1995, indicates that the efficiency of gene transfer into stem cells was much lower when similar protocols were assessed in large mammals and in human gene therapy trials, suggesting that there are species-specific differences in the susceptibility of stem cells to retrovirus infection" (p. 58, column 1). There are no working examples in the specification which indicates the efficiency of transduction in bone marrow stromal or stromal stem cells of any mammal including humans wherein a therapeutic effect is generated.

Thus, it is clear from the evidence of record that that *ex vivo* gene therapy as claimed is not reasonably predictive and not yet shown to be successful. Applicants have not provided any convincing evidence that their claimed invention is indeed useful as a therapeutic for the treatment of any obese disorder or condition as listed or contemplated by the as-filed specification, and have not provided sufficient guidance to allow one skilled in the practiced the claimed invention without undue experimentation for the contemplated use of the claimed product as recited in claim 77. In absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

In view of the lack of guidance regarding the administration parameters, lack of working examples, breadth of the claims, state of the art and the unpredictability of the art, as set forth by the evidence presented above, undue experimentation would be required by one of ordinary skill to practice the invention in the context of therapeutic application of the claimed cells in the treatment of obesity in any animal at the time the invention was made.

Cancellation of claim 77 would obviate the entire rejection under 35 USC 112, first paragraph.

In view of the newly found prior art, the following prior art rejection is applicable. Note that is the examiner's position that the claimed implantable container and/or a general method using the container for a simple delivery of any secreted protein encoded DNA do not necessarily require to exhibit any therapeutic effect produced by the expressed secreted proteins in human patients. As such and insofar as the claims are readable on the making and use of the claimed container which can be used for a variety of purposes, *e.g., in vitro* use for screening a variety of compounds, model systems for the study of physiologic or pathologic conditions, see US Pat No. 5,858,721, columns 14 and 15, for example, the following prior art rejection is applicable.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 69-71, 99-108, 112, and 113 are rejected under 35 USC 103(a) as being unpatentable over

Naughton, Somatic Cell and Molecular Genetics, Vol. 18, No. 5, pp. 451-462, 1992, taken with any of Naughton *et al.* (US Pat No. 5,858,721), Caplan *et al.* (US Pat No. 5,197,985), Schinstin *et al.* (US Pat No. 5,843,431), Mardon (previous cited prior art), and as evidenced by applicant's admission of the prior art of record as indicated on page 6 bridging page 7, and page 27 of the specification.

Naughton teaches a method of using cultured bone marrow stromal cells associated with a polymeric matrix for implantation and providing a protein of interest to a cell in a mammal for research in animal models such as rats (page 460, column 2, last paragraph, page 461, column 2), wherein the cells are genetically modified cells to express a recombinant protein of interest. The *in vivo* data shows that the percentage of reporter gene expressing rat bone marrow cells at 90 days after grafting was significantly greater than that observed at 45 days (page 460, column 2).

In addition, vectors containing regulatory sequence operably linked to a transgene of interest including a marker is routine and conventional in the art for cell trasnfection and would have been obvious as minor modifications, as evidenced by Naughton. Naugton does teach the use of a microcarrier, diffusion chamber, or microcapsule to control and/or enhance the delivery and release of the isolated bone marrow stromal cells.

However, at the time the invention was made, the prior art of record, as exemplified by Naughton *et al.*, Caplan, Schinstin *et al.*, and Mardon, does teach that it is routine and conventional to use a microcarrier, diffusion chamber, or microcapsule to enhance the delivery and subsequent release and differentiation of the implantable mesenchymal stem cells to the target site (see entire document of each of the cited reference). Furthermore, the specification teaches on page 3 bridging page 7 that immunological isolation means include well known technologies and devices such as microencapsulation, diffusion chambers, etc.

It would have been obvious for one of ordinary skill in the art to have employed any known a microcarrier, diffusion chamber, or microcapsule to enhance the delivery and subsequent release of the implantable bone marrow stromal cells disclosed in Naughton to the target site. One of ordinary skill in the art would have been motivated to have employed a microcarrier, diffusion chamber, or microcapsule to enhance the delivery and subsequent release of the implantable bone marrow stromal cells to the target

site because of the reasons set forth in the immediately preceding paragraph. Note that use of well known technologies and devices such as microencapsulation, diffusion chambers, etc., as taught by the combined cited references, would physically isolate the isolated genetically modified stromal cells from the immune response, as evidenced by applicant's admission of the prior art of record as indicated on page 6 bridging page 7 of the specification.

In addition, one of ordinary skill in the art would have been motivated to transfect or transduce the cells of Naghton by conventional methods with vectors containing any known promoter, signal sequences, beneficial protein, and/or a coding sequence of a selectable marker, such as those disclosed in the cited references to determine and track the effect of these regulatory elements and the subsequent expression of a desired gene during the differentiation of the stromal cells once implanted in an animal model.

It would also have been obvious for one of ordinary skill in the art to have employed any pore size in any of the containers available in the prior art of record as an obvious matter of design choice particularly since such modifications would be expected to lead to an equivalent enhancement in delivery, release, expression and differentiation of the cells at the target delivery site, particularly in view of the absence of factual evidence showing an unexpected property of the use of the claimed pore size relative to those outside the claimed diameter of the pores of the claimed containers.

Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's response has been considered by the examiner but is moot in view of the new grounds of rejection as set forth above.

Gilbert, Transplantation, Vol. 56, 2, pp. 423-427, 1993, is cited to provide evidence demonstrating that even in 1993, carriers composed of biodegradable polymer scaffolds have been used routinely and successfully to study the delivery and expression of a therapeutically useful product in rats, and such study along with other cited references do show that at the time the invention was made, it is very common to those skilled in the art to actively employ improved biodegradable and/or biocompatible carriers to enhance gene delivery and expression of therapeutic protein products in *in vivo* experimental models, even though a

therapeutically relevant effect has not been proven in any mammal having a naturally occurring disease or disorder intended for the treatment in the real-world.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER